

REMARKS

Claim 1 has been amended to add the term "in vitro;" claim 2 has been amended to remove the term "is" and claim 3 has been amended to replace the term "the" with "an." Similarly, claim 4 has been amended to correct a typographical error. The amendments are fully supported by the original claims and the specification and do not contain new matter. Claims 7-8 have been withdrawn by the Examiner as non-elected.

The Applicants expressly rebut any presumption that the Applicants have surrendered any equivalents under the doctrine of equivalents and expressly state that the claims, as amended, are intended to include and encompass the full scope of any equivalents as if the claims had been originally filed and not amended.

Claim Rejections Under 35 USC § 112, 1st Paragraph: Indefiniteness

Claims 1-3 have been rejected under 35 USC §112, first paragraph for indefiniteness. According to the Examiner, there is insufficient antecedent basis for the "are/is" limitation in claim 2 and for "the" alphavirus limitation in claim 3. In response, the Applicants note that the claims have been amended to replace the "are/is" in claim 2 with "are" and "the" alphavirus term in claim 3 with "an." In addition, with respect to claim 1, the Applicants note that the term "or" is a definite term used in many claims allowed by the U.S. Patent and Trademark Office and should not be rejected under 35 U.S.C. § 112 for indefiniteness. Accordingly, the Applicants respectfully request that this rejection be withdrawn.

Claim Rejections Under 35 USC § 112, 1st Paragraph: Lack Of Enablement

Claims 1-6 are rejected under 35 USC §112, first paragraph, for lack of enablement. According to the Examiner, the specification does not reasonably provide

enablement for the in vivo inhibition of the expression of any target gene in cells or tissues by administering the viral particles of the present invention.

In response, the Applicants have amended the claims to recite a "process for inhibiting expression of a target gene in cells or tissue in vitro." Accordingly, the Applicants respectfully request that the rejection under 35 USC §112 be withdrawn.

Claim Rejections Under 35 USC § 102

Claims 1-2 and 4-6 are rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,506,559 ("Fire"). The Examiner asserts that Fire teaches: (1) a process for inhibiting the expression of a target gene in cells or tissues (citing col. 6, lines 32-45) by administering RNA which comprises homologous nucleotide sequences to a portion of the target gene (citing col. 7, lines 53-68); (2) that the double stranded structure can be formed by two complementary RNA strands inside the cell (citing col. 7, lines 42-53); (3) that the RNA can be introduced into a cell by a viral construct packed into a viral particle (citing col. 9, lines 49-55); (4) that the length of the homologous nucleotide sequence is at least 50 bases in length (citing col. 8, lines 1-5); and (5) that the target gene may be eukaryotic, viral, or synthetic (citing col. 8, lines 12-63) and the target gene may be a developmental gene, oncogene, a tumor suppressor gene or an enzyme (citing col. 11, lines 8-37). In addition, the Examiner asserts that while Fire does not disclose cells that are infected with equal amounts of viral particles, this would (according to the Examiner) be inherent in order to form an RNA duplex from two complementary strands. For the following reasons, the Applicants respectfully traverse this rejection.

First, the Fire patent issued on January 14, 2003 and therefore cannot be a prior art reference under 102(b) since the Applicants claim the benefit of the filing date of November 29, 2000.

Second, the Fire patent does not disclose all the elements of each claim rejected. In order for a reference to anticipate a claim under 35 U.S.C. § 102, the reference must disclose every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently, in a single prior art reference." See MPEP § 2131.

Here, Fire fails to disclose at least two elements common to all of the claims. Fire does not disclose: (1) infecting cells or tissue with a set of viral particles of single stranded RNA expressing the sense RNA strand (instead of the anti-sense strand); and (2) infecting cells or tissue with a set of viral particles of single stranded RNA expressing the anti-sense RNA strand (instead of the sense strand). See Fire at column 9, lines 49-55 as cited by the Examiner (no teaching of two separate sets of viral particles). In addition, there is no other teaching in Fire that mentions using viral particles as a delivery method.

Accordingly, because Fire fails to disclose the above elements either expressly or inherently, the rejection under 35 U.S.C. § 102 should be withdrawn.

Claim Rejections Under 35 USC § 103

Claims 1 and 3 are rejected under 35 U.S.C. § 103 as being unpatentable over Fire in view of Johanning et al., Nucleic Acids Research 1995, Vol. 23(9): 1495-1501 ("Johanning"). The Examiner asserts that although Fire does not teach that the viral construct consists of an alphavirus, Johanning discloses an alphavirus vector that is capable of expressing a single stranded RNA transcript in cells (citing page 1498, col. 2). Thus, according to the Examiner, it would have been obvious to one of ordinary skill in the art to substitute the alphavirus vector construct, as taught by Johanning for the generic viral vector, as taught by Fire. The Applicants respectfully traverse this rejection for the following reasons.

A. No Prima Facie Case of Obviousness Has Been Established

First, a *prima facie* case of obviousness has not been established because: (a) Fire (taken alone or in combination with Johanning) does not teach or suggest all the claim limitations; and (b) there is absolutely no motivation to modify Fire to obtain the presently claimed invention.

1. Fire Alone Or In Combination With Johanning Does Not Teach Or Suggest All Of The Claim Limitations

Fire (taken alone or in combination with Johanning) does not teach or suggest all the claim limitations of each claim. Under MPEP § 2143.03 in order to establish a *prima facie* case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. If the prior art references do not disclose or suggest all of the claim limitations either by themselves or in combination with each other, there can be no *prima facie* case of obviousness.

Here, neither Fire or Johanning teach or suggest at least two important limitations common to all of the claims of the present invention which are: (1) infecting cells or tissue with a set of viral particles expressing sense RNA and (2) infecting cells or tissue with a separate set of viral particles expressing anti-sense RNA. There is simply no teaching or suggestion in either Fire or Johanning of the above claim limitations of the present invention. As stated above, Fire at column 9, lines 49-55, only discloses that a viral construct packaged into a viral particle may introduce an expression construct into the cell and transcription of RNA encoded by the expression construct. There is no other teaching or disclosure in Fire that even mentions viral particles. Similarly, Johanning only teaches the use of a self-replicating RNA vector system wherein the RNA construct encodes sindbis virus non-structural proteins required for RNA replication and transcription (Johanning at p. 1496, 1st column). Accordingly, there is no teaching in Fire or Johanning that discloses the use of two separate viral particle populations (wherein one population provides the sense strand

instead of the anti-sense strand and the other provides the anti-sense strand instead of the sense strand).

Thus, Fire (taken alone or in combination with Johanning) does not teach or suggest all the claim limitations for each claim of the present invention. Accordingly, a *prima facie* case of obviousness has not been established for this reason alone.

2. There is No Motivation To Modify Fire Or To Combine Johanning With Fire

There is absolutely no motivation to modify Fire to obtain the presently claimed invention or to combine Johanning with Fire. "To establish a *prima facie* case of obviousness . . . there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference." See MPEP § 2143.01, entitled "Basic Requirements of a *Prima Facie* Case of Obviousness."

Here, the Examiner has presented no evidence establishing a proper motivation to combine Johanning with Fire or to modify the viral particles mentioned in Fire into 2 separate sets of particles (one expressing sense RNA and the other expressing anti-sense RNA). Under MPEP §2143.01, "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination" and the "fact that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish *prima facie* obviousness The level of skill in the art cannot be relied upon to provide the suggestion to combine [or modify] references").

In addition, as stated above, combining Johanning with Fire does not cure the deficiencies of Fire (all the claim limitations would still not be taught or suggested by the combination). Thus, even if a motivation was found to combine Johanning with Fire, Johanning adds nothing with respect to a motivation to modify the viral particles

mentioned in Fire into 2 separate sets of viral particles (one providing sense RNA and the other providing anti-sense RNA).

Accordingly, no motivation has been established to modify Fire to obtain the present invention. Thus, a *prima facie* case of obviousness has not been established for this reason alone.

B. There Are Surprising And Unexpected Results

The Examples of the present application surprisingly demonstrate that when the sense and anti-sense fragments are provided by different vectors there is an inhibition of the expression of chromosomal cyclin genes. In contrast, when both sense and anti-sense fragments are provided in the same construct in the same vector inhibition of the expression of chromosomal cyclin genes does not occur (see Examples 6 & 7 on page 15 of the specification). Under MPEP § 2144-45, evidence of such surprising and unexpected results rebuts a *prima facie* case of obviousness.

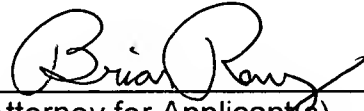
All of the claims of the present invention require that cells or tissue be infected by two different sets of viral particles: one set providing the sense RNA and the other providing the anti-sense RNA. As shown in Example 7 (page 15 of the specification), when both sense and anti-sense sequences are cloned into the same construct in the same vector, there was no inhibition of the target gene(s) after infection. In contrast, as shown in Example 6, when the sense and anti-sense sequences are cloned separately into separate vector populations, there was inhibition of the target gene(s) after infection (which was even more potent than inhibition of cell growth by antibiotics [neomycin and zeocin], see page 15 of the specification). This represents surprising and unexpected results. Accordingly, regardless of whether or not a *prima facie* case of obviousness has been established, these surprising and unexpected results rebut any assertion that the claimed invention is obvious.

For all of the above reasons, the Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

Conclusion

Entry of the foregoing remarks and amendments is respectfully requested. No fee is believed to be due in connection with the filing of this Amendment. However, if any fee is deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,

A handwritten signature in cursive script, appearing to read "Brian Remy", is written over a horizontal line.

Attorney for Applicant(s)
Brian C. Remy
(Reg. No. 48176)
340 Kingsland Street
Nutley, NJ 07110
Telephone (973) 235-6516
Telefax: (973) 235-2363

158116